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Pulmonary artery pressures in prematurely born children at school age

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List of Abbreviations: BPD-Bronchopulmonary dysplasia; CMV-Conventional mechanical ventilation; EDIVS-End diastolic diameter of the inter-ventricular septum; EP-Extremely premature; HFO-High frequency oscillation; LA-Left atrium; LVEF-Left ventricle ejection fraction; LVEDD-End diastolic diameter of left ventricle; MPAP-Mean pulmonary artery pressures; MV-Mitral valve; NO-Nitric oxide; PH-Pulmonary hypertension; PMA-Postmenstrual age; RA-Right atrial; RV-Right ventricular; SGA-Small for gestational age; SPAP-Systolic pulmonary artery pressure; TR-Tricuspid regurgitation; TV-Tricuspid valve, FEV_1 - forced expiration volume of air exhaled in the first second, FVC - forced vital capacity, FEF_{25}- forced expiratory flow at the 25% of exhaled FVC, FEF_{50}- forced expiratory flow at the 50% of exhaled FVC, FEF_{75}- forced expiratory flow at the 75% of exhaled FVC, FEF_{25-75} - The mean forced expiratory flow between 25% and 75% of the FVC

ABSTRACT

Objectives: To test the hypothesis that pulmonary artery pressures were higher in school aged children born extremely prematurely (EP) than those born at term. We also wanted to assess if pulmonary artery pressures differed between prematurely born children with or without bronchopulmonary dysplasia (BPD) or between those randomized in the neonatal period to different ventilation modes.

Study design: Transthoracic echocardiography was performed on 193 EP children (106 had BPD) and 110 term born children when they were 11-14 years of age. Ninety-nine EP children had been supported by high frequency oscillation and 94 by conventional ventilation. Tricuspid regurgitation (TR) was assessed in the apical four-chamber and modified parasternal long axis views. Continuous-wave Doppler of the peak regurgitant jet velocity was used to estimate the right-ventricular-to-right-atrial systolic pressure gradient.

Results: TR was measurable in 71% (137/193) of the preterm and 75% (83/110) of the term born children (p 0.23). The prematurely born compared to the term born children had a higher peak TR velocity (2.21 versus 1.95 m/s, $p<0.001$) and the prematurely born children who had BPD versus those without BPD had a higher peak TR velocity ($p=0.023$). There were no significant differences in pulmonary artery pressures according to neonatal ventilation mode.

Conclusions: Pulmonary artery pressures were estimated to be higher in 11-14 year olds born extremely prematurely compared to those born at term and in those born prematurely who developed BPD compared to those who did not, but did not differ significantly by neonatal ventilation mode.

INTRODUCTION

Pulmonary hypertension (PH) appears to be common in very low birth weight infants. In one series, 18% of infants had PH during their time on the neonatal intensive care unit (NICU) (1). Those with bronchopulmonary dysplasia (BPD) or who were born small for gestational age (SGA) were most likely to be affected. In certain infants, high pulmonary pressures persisted beyond discharge from the NICU (1-4). There is, however, conflicting evidence regarding whether PH persists into later childhood in those born prematurely. In one study, children who had had BPD, when assessed at two to four years of age had a decreased pulmonary artery acceleration time and left and right ventricular myocardial performances consistent with higher pulmonary artery pressures and impaired biventricular systolic and diastolic function (5). Mourani et al evaluated ten patients who had had BPD and found at cardiac catheterization at a median age of ten years, elevated mean pulmonary artery pressures (MPAP) (6). There are limited data on pulmonary artery pressures of prematurely born children, particularly those who did not develop BPD.

An aim of this study was to test the hypothesis that pulmonary artery pressures at 11-14 years of age would be higher in those born extremely prematurely (that is less than 29 weeks of gestation) compared to those born at term. In addition, we wished to determine whether pulmonary artery pressures differed between those who had or had not BPD. Amongst children born extremely prematurely, we have demonstrated that a neonatal ventilation mode, high frequency oscillation (HFO) was associated with better lung function at 11-14 years of age (7). The children had been entered into a randomized trial of two neonatal ventilation modes, the United Kingdom Oscillation Study (UKOS) (8). There is a significant interaction between pulmonary blood vessels and branching airways during lung development (9).

Hence, we further aimed to test the hypothesis that the HFO group would have lower pulmonary artery pressures than the group supported by conventional ventilation.

METHODS

Term and preterm groups of children were assessed separately, at 11 to 14 years of age. The prematurely born children were part of the United Kingdom Oscillation Study (UKOS) (7, 8). Term born children were recruited from local schools in South London. All participants were assessed at a single centre (King's College Hospital NHS Foundation Trust, London). Assessments of preterm children were done in the time period from the end of July 2011 until the end of February 2013 (Figure 1; on line). Term children were assessed from June 2013 until the end of February 2014 (Figure 2; on line). Children were excluded from analysis if found to have a structural congenital heart or lung condition, or if they were acutely unwell at the time of assessment. The study was approved by the South West London National Research Ethics Service Committee and parents gave informed, written consent for their child to take part. At assessment, the children's height, weight and blood pressure were measured. Blood pressure was measured using vital signs monitor with a paediatric blood pressure cuff of appropriate size. Oxygen saturation assessments were obtained by pulse oximetry.

Echocardiography

Two-dimensional echocardiography was performed using a Phillips iE33 ultrasound device, equipped with standard 5 and 8 MHz transducers. Multiple views were recorded including subcostal long axis, apical four-chamber, parasternal long axis, parasternal long axis angulated for tricuspid valve (TV) and parasternal short axis views. In the apical four-

chamber and the parasternal long axis angulated views colour Doppler was used to look for tricuspid regurgitation (TR). The reproducibility of the measurements was assessed on 20 scans, reviewed independently by a paediatric cardiology consultant (KP) and the research fellow (SZ). If present, continuous wave Doppler was used to look at the TR Doppler profile. In the presence of a complete TR envelope throughout systole, the time-velocity integral was traced to obtain the peak and mean systolic right-ventricular-right-atrial (RV-RA) gradients using the modified Bernoulli equation (10). Two pulmonary artery pressure indices, the systolic pulmonary artery pressure (SPAP) and mean pulmonary artery pressure (MPAP) were derived from the peak and mean systolic RV-RA gradients.

To assess the right atrial pressure (RAP), the IVC diameter was measured two centimeters from the IVC-RA junction. The child was asked to perform one brief rapid inspiration and IVC collapse was recorded. When the IVC diameter was less than two centimeters and the collapsibility was greater than 50%, the RAP was estimated as 5 mmHg and as 10 mmHg when the collapsibility was less than 50%. When the IVC diameter was greater than two centimeters, the RAP was estimated as 15 mmHg when the collapsibility was greater than 50% and as 20 mmHg when the collapsibility was less than 50% (10). Measurements of IVC diameter in children have been found to correlate with RAP measured by cardiac catheterization, however the IVC collapsibility had no significant association with RAP (11). Hence, the SPAP was calculated by adding to the peak systolic RV-RA gradient assuming a right atrial (RA) pressure 5 mmHg in all cases. The MPAP was calculated as the mean RV-RA gradient plus RAP assumed to be 5 mmHg in all cases (12). Measurements of RAP from the collapsibility and diameter of the IVC were compared between groups independently from the TR measurements. Pulmonary artery hypertension was defined as the systolic pulmonary artery pressure (SPAP) greater than 36 mmHg, calculated from the peak TR

velocity which was equal or greater than 2.8 m/s, as per ERS guidelines (13). The children with an SPAP of 30 mmHg or less were divided into two groups; those with a SPAP less than 25 mmHg (low SPAP) and those with an SPAP of 30-25 mmHg (moderate SPAP). Additional measurements of the pulmonary artery pressure, independent of tricuspid regurgitation velocity, were undertaken, that is the pulmonary end diastolic pressure estimated from pulmonary regurgitation jet and the pulmonary artery acceleration time (PAAT) (14). RV systolic function was estimated by calculating tricuspid annular plane systolic excursion (TAPSE) using the M-mode measurement of the systolic long axis motion of the RV free wall in the apical four chamber view (15-17). To exclude secondary pulmonary hypertension caused by left atrial hypertension, a number of left sided measurements were made. These included left atrium (LA) dimensions measured in the apical four chamber view at the end of ventricular systole. Mitral valve (MV) inflow velocities, the ratio of the early filling and atrial filling velocities of the left ventricle (E:A wave ratio), were determined. The end diastolic diameter of the left ventricle (LVEDD), left ventricle ejection fraction (LVEF) and end-diastolic diameter of the inter-ventricular septum (EDIVS) were measured from the M-mode recorded at the tip of the mitral valve leaflets in the long parasternal view. The parasternal short axis views were inspected and recorded at the level of mitral valve leaflets to exclude RV dilatation (12, 18).

Spirometry

Large-airway and small-airway function was assessed by spirometry, Measurements of forced expiratory flow in the first second (FEV_1) and at 25%, 50% and 75% (FEF_{25}, FEF_{50}, FEF_{75}) of the expired vital capacity (FVC) were obtained. A Jaeger MS-PFT Analyzer Unit was used. The measurement was considered reproducible if three technically satisfactory volume-time loops were obtained with FEV_1 and FVC measurements within 6% of each

other (19). The results were expressed as the percentage predicted for height and weight using established reference ranges and converted into z scores as appropriate (20).

Sample size calculation

The sample size for the prematurely born cohort was fixed as the children were followed up at age 11-14 years from the UKOS trial (7). Post hoc power calculation for the differences in pulmonary pressures was done for the peak velocity of the tricuspid regurgitation (TR vmax (m/s)), assessed by continuous wave Doppler as the primary outcome. The achieved sample size of 110 children in each group allowed a difference of one standard deviation to be detected with 90% power at the 5% significance level. Difference in pulmonary pressure of 3 mmHg (equal to difference in velocity of 0.9 m/s) is considered significant in predicting the clinical outcome (13, 21, 22).

Analysis

Differences were assessed for statistical significance using the student t test, the Mann-Whitney U test or Chi-square test as appropriate. A sensitivity analysis was performed for birth weight and gestational age for all echocardiographic parameters. As the perinatal data of the term children were incomplete, a separate analysis was performed to compare the term and preterm children with available data on gestational age and birth weight. All echocardiographic and spirometry results were adjusted in the regression analysis for observed baseline imbalances at the time of assessment, that is the differences in age and height between the preterm and term groups; analysis of covariance was performed. Three group comparisons were performed for all echocardiographic measurements (preterm

children with previous BPD, preterm children without BPD and term born children). One-way ANOVA was used to assess the influence of BPD diagnosed as oxygen requirement at 36 weeks corrected gestational age. The analysis was performed using SPSS 22 version (SPSS GmbH Software – IBM Company).

RESULTS

Two hundred prematurely born children were assessed. Seven were excluded from the analysis. One child had a large atrial septum defect, one had a clinically significant persistent ductus arteriosus, one was diagnosed with hypertrophic cardiomyopathy at the time of screening, two had severe scoliosis and two had a poor window quality on ECHO assessment. One hundred and six of the prematurely born children had had BPD, defined as oxygen dependency beyond 36 weeks PMA. One hundred and thirteen term born children were assessed. Three were excluded from the analysis: one child had had a congenital diaphragmatic hernia, one had severe nephrotic syndrome with a pericardial effusion and one was discovered at assessment to have been born prematurely.

The prematurely born compared to the term born children at assessment had a lower age ($p = 0.02$) and height ($p<0.001$), (Table 1). The mean oxygen saturation, although in the normal range in both groups, was higher in the term born children ($p = 0.008$) and the systolic and the diastolic blood pressure lower in the prematurely born children ($p<0.001$) (Table 1). The TR velocity jet was present and measurable in 71% (137/193) of preterm and 76% (83/110) of term children, $p=0.23$. There was moderate to substantial agreement on the assessment of TR between the two assessors (Kappa statistic 0.69). In the preterm population, one child had an SPAP of 36 mmHg and four children had an MPAP equal or

above 25 mmHg, but none of the term children were so affected ($p<0.001$). There were also significant differences in the proportions of preterm and term children with a low SPAP (<25 mmHg) (51% preterm versus 87% term) or a moderate SPAP (25-30 mmHg) (40% preterm versus 13% term) ($p<0.001$, $p<0.001$ respectively).

The peak TR velocity, the peak and mean RV-RA gradient, the estimated RA pressure and the calculated SPAP and the MPAP were significantly higher in the prematurely born children (Table 2). The mean TAPSE was significantly lower in the prematurely born children compared to the term children, although the ranges in both groups were within normal limits. The ejection fraction of the left ventricle was higher in the preterm group in comparison with the term born children (68.7% vs 64.8%, $p=0.001$) (Table 2).

There were no significant differences in left atrial size, left ventricle end diastolic diameter or the diastolic function of the left ventricle (E/A ratio) between the prematurely and term born groups (Table 2). There was, however, a significantly lower inter-ventricular septum end diastolic diameter in the prematurely born children (Table 2). Additionally, there was significantly higher end diastolic velocity of the pulmonary regurgitation in the prematurely born children ($p=0.046$), (Table 2). Pulmonary artery acceleration time was shorter in children born preterm, however this was not statistically significant after adjusting for age and height at the time of assessment (Table 2). When the sensitivity analysis for birth weight and gestational age, the differences between the preterm and term born groups remained statistically significant for all the cardiac results except the LVEF (%) (Table 2).

All the lung function results of the preterm children were significantly lower than the term born children (Table 2). A mean difference in FEV_1 z score of -0.78 SD was found between

term and preterm groups, $p<0.001$. There was also significantly reduced FEV_1/FVC z score in preterm children (mean difference 1.06 SD, $p<0.001$) and reduced PEF % predicted (mean difference 12.7%, $p<0.001$), (Table 2). Preterm children also had lower small and medium airway function, with significant differences in FEF_{25} z score, FEF_{50} z score, FEF_{75} z score and FEF_{25-75} z score (mean difference in FEF_{25-75} z score 0.9 SD, $p<0.001$) (Table 2).

Preterm children who had had BPD had a significantly lower mean gestational age at birth and birth weight and lower oxygen saturation levels at assessment than preterm children without BPD (Table 3). Comparison of the results of those born prematurely who did or did not develop BPD demonstrated those who had had BPD had significantly higher mean TRvmax ($p=0.023$) and significantly lower mean LVEF ($p=0.006$) (Table 4). In addition, children who had developed BPD had significantly lower FEF_{50} (p 0.04) and FEF_{25-75} z-scores (p 0.04), (Table 4).

There were no significant differences in the demographics or the echocardiographic results between the prematurely born children who had been supported by HFOV or CMV (Table 5).

DISCUSSION

We have demonstrated that at 11-14 years of age, the mean pulmonary pressures of extremely preterm children were higher than those of children born at term. Only one of the children born prematurely, however, had a systolic pulmonary pressure of 36 mmHg, measured by SPAP and, therefore, fulfilled the diagnosis of pulmonary hypertension according to ERS guidelines (13).

In addition to the pulmonary pressures being higher in prematurely born children, they also had lower right ventricular systolic function as measured by TAPSE. The differences remained significant after adjusting for differences in age and height between those born at term or prematurely. Our results suggest that higher pulmonary pressures in the preterm children had affected the systolic function of their right ventricle, even in the absence of pulmonary hypertension.

It is interesting that the higher pulmonary artery pressure and right ventricular afterload did not cause an increase in RV septal wall thickness. Indeed, the prematurely born children had a thinner septum, although still within normal z score range. A possible explanation is the lower blood pressures of the prematurely born children. In addition, the systolic afterload of the left ventricle is a more important determinant of septal thickness.

Our results contrast with those of Joshi et al (22). In their study, no significant differences at 8-12 years of age were found in right and left ventricular function between 90 children either born at term or prematurely. Sixty of the children were born at less than 33 weeks of gestation, but only 28 had had BPD. No significant differences were found in right and left ventricular function between those with or without BPD. The sample size, however, was based on a difference in the response of the pulmonary artery pressures to hypoxia (22).

There is evidence that preterm birth is associated with global myocardial structural and functional differences in adult life with potentially clinically significant impairment in right ventricular systolic function (23, 24). In a study of 102 young adults born prematurely, smaller right ventricular size was found on cardiovascular magnetic resonance, when

compared to term born individuals. Furthermore, 21% of the young adults had ejection fractions of the right ventricle below the lower limit observed in adults born at term (24). The changes in the right ventricle were greater than those previously observed in the left ventricle (20). Unfortunately, the above study did not provide simultaneous data on the pulmonary pressures. It is possible, however, that the structural changes detected in adulthood could be a consequence of an increase in pulmonary artery pressures.

In a recent study by Aye and co-workers, TAPSE was found to be reduced at birth and at three months of age in moderately prematurely born infants, that is born at a gestational age of 34 weeks. The main finding of the study was a disproportionate increase in the ventricular mass in the children suggesting that preterm birth had altered the growth pattern of cardiomyocytes from hyperplastic to hypertrophic. It was, however, not possible to exclude maternal hypertension during pregnancy as a potential influencing factor on the myocardium (25).

Similar to our findings, a smaller study has found significantly thinner intra ventricular septum in infants born preterm (31 to 34 weeks GA) when compared to term infants. In addition, there was reduced ventricular diastolic function measured by tissue Doppler imaging (26).

Reduced right ventricular function can potentially indicate the severity and chronicity of increased pulmonary artery pressure. The possible mechanism underlying the decrease in systolic function of the right ventricle secondary to increased pulmonary artery pressure has been previously described (27-29).

Injury to the small airways in infants born extremely preterm have been previously described (30). Our study has shown significantly reduced small airway function in children born extremely preterm when compared to those at term, children who had previously had BPD being more affected. Higher pulmonary pressures may imply that small pulmonary arteries were also affected, suggesting a common underlying mechanism of injury such as inflammatory process, including perivascular and interstitial inflammation (31). In addition, abnormal pulmonary vessels could potentially affect the function of their adjacent airways (32).

Previous studies of children born prematurely have usually concentrated on those with BPD (6, 33). In our study, 55% of the preterm children had had BPD. We demonstrated that the children, who had BPD compared to those who did not, had significantly higher TRvmax. Those findings are supported by earlier results showing that infants with severe BPD when examined at a median age of 12 months had raised pulmonary vascular resistance (34). It is important, however, to note that in this study both prematurely born groups had significantly worse mean TRv_{max}, SPAP, MPAP and TAPSE than the children born at term demonstrating it is important to follow up children born extremely prematurely regardless of a previous diagnosis of BPD.

Comparison of pulmonary artery pressure results demonstrated no statistical differences between children who had been supported by CMV or HFOV. There were also no significant differences in left atrial dimensions, intra-ventricular septum diameter, left ventricular systolic and diastolic function or right ventricular systolic function between the

two ventilation groups. A possible explanation is that although there were highly significant differences in the lung function of the two groups at 11 to 14 years, the difference was relatively small (7). It may be, however, as these children go through puberty, differences in lung function may become greater and then be associated with differences in pulmonary pressures and other echocardiographic results. It is possible that any differences in lung function post puberty will be particularly marked in the females (35). Amongst young adults who had had BPD, females but not males had worse lung function and more respiratory symptoms than term born controls. The authors suggested this was due to greater chest wall growth in the males during puberty (35).

This study has a number of strengths and some limitations. The study is the largest study to date measuring pulmonary artery pressures in very preterm children at school age. The feasibility of the TR measurement was consistent with the literature and an extensive suite of assessments was undertaken. As the term born children were recruited after the preterm groups' assessments had finished, the sonographers were not blinded to whether the children were term or preterm. They were, however, blinded to all the perinatal factors of the preterm children including their ventilation group and BPD status. In our study, the children did not undergo cardiac catheterization and this may be considered to be a limitation. Examination by echocardiography can underestimate or overestimate SPAP in comparison with the gold standard cardiac catheterization (10, 36, 37) nevertheless it has been suggested to be a valuable screening tool. The clinical utility of echocardiography (ECHO) in the diagnosis of the pulmonary vascular disease in children with BPD has been described by Mourani et al (33). They assessed 29 patients with BPD who had an ECHO in the first two years after birth who subsequently underwent cardiac catheterization. Tricuspid regurgitation was detectable in 19 children, allowing estimation of the systolic pulmonary artery pressure (SPAP) in 61%

of the patients. Cardiac catheterisation confirmed pulmonary hypertension in 23 of the 29 patients (33). As our study was limited to 2D echocardiography, it was not possible to measure the 3D size of the RV and LV, and therefore changes in the RV wall thickness could not be assessed. The literature suggests the difference of 3 mmHg in pulmonary pressures could be potentially significant in determining the clinical outcomes (13). We report a difference of 4 mmHg obtained through measurements of the systolic RV-RA gradient. A limitation of our study is that we did not assess exercise tolerance and thus cannot comment on the clinical significance of our findings. Our recommendation for future follow up of similar cohorts would be to formally assess exercise tolerance.

CONCLUSION

In conclusion, children born very prematurely have significantly higher mean pulmonary artery pressures at school age when compared to term children, but there was no influence of neonatal ventilator mode. In addition, the prematurely born children had lower systolic function of the right ventricle and thinner inter ventricular septum. The clinical significance of the raised pulmonary artery pressures in the prematurely born children and whether with increasing age the pulmonary artery pressures will further increase is not known. It is, therefore, crucial this cohort is re-examined after puberty.

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FIGURE LEGENDS FOR ON LINE SUPPLEMENT

Figure 1: UKOS recruitment flow diagram for ECHO analysis between ventilation groups

Figure 2: UKOS recruitment flow diagram for ECHO analysis between gestation groups (term vs preterm)